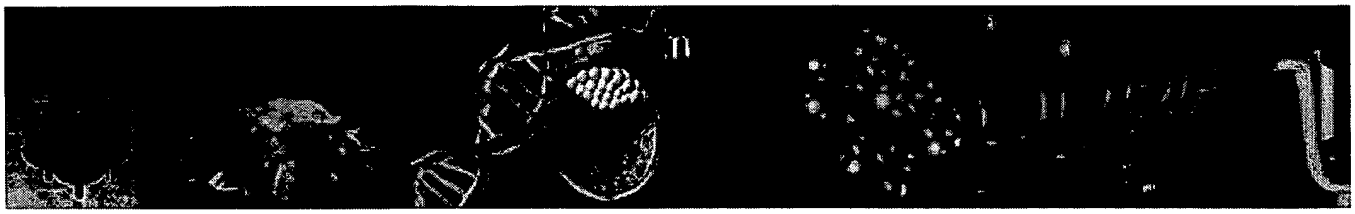
Reproductive & Cardiovascular Disease Research Group



APOPTOSIS
Caspases

Introduction Substrates Apoptosome

Caspases are a family of proteins that are one of the main effectors of apoptosis.The caspases are a group of cysteine proteases that exist within the cell as inactive pro-forms or zymogens. These zymogens can be cleaved to form active enzymes following the induction of apoptosis.

Induction of apoptosis via death receptors results in the activation of an initiator caspase such as caspase 8 or caspase 10. These caspases can then activate other caspases in a cascade. This cascade eventually leads to the activation of the effector caspases, such as caspase 3 and caspase 6. These caspases are responsible for the cleavage of the key cellular proteins that leads to the typical morphological changes observed in cells undergoing apoptosis. A list of the main caspases and some of their substrates is shown in the table below.

Caspase	Alternate name	Substrates	Function (and notes)
Caspase-1	ICE	pre-Interleukin-1β Interleukin-18 Lamins	Processing of interleukins (inflammation). Can also induce apoptosis depending on isoform and if overexpressed.
Caspase-2	Ich-1 (human), Nedd2 (rat, mouse)	Golgin-160 Lamins (?)	Apoptosis (activity supressed by serum deprivation)
Caspase-3	CPP32, Yama, apopain	PARP SREBs Gelsolin Caspase-6 Caspase-7 Caspase-9 DNA-PK MDM2 Gas2 Fodrin β-Catenin Lamins NuMA	Apoptosis

SEARCH

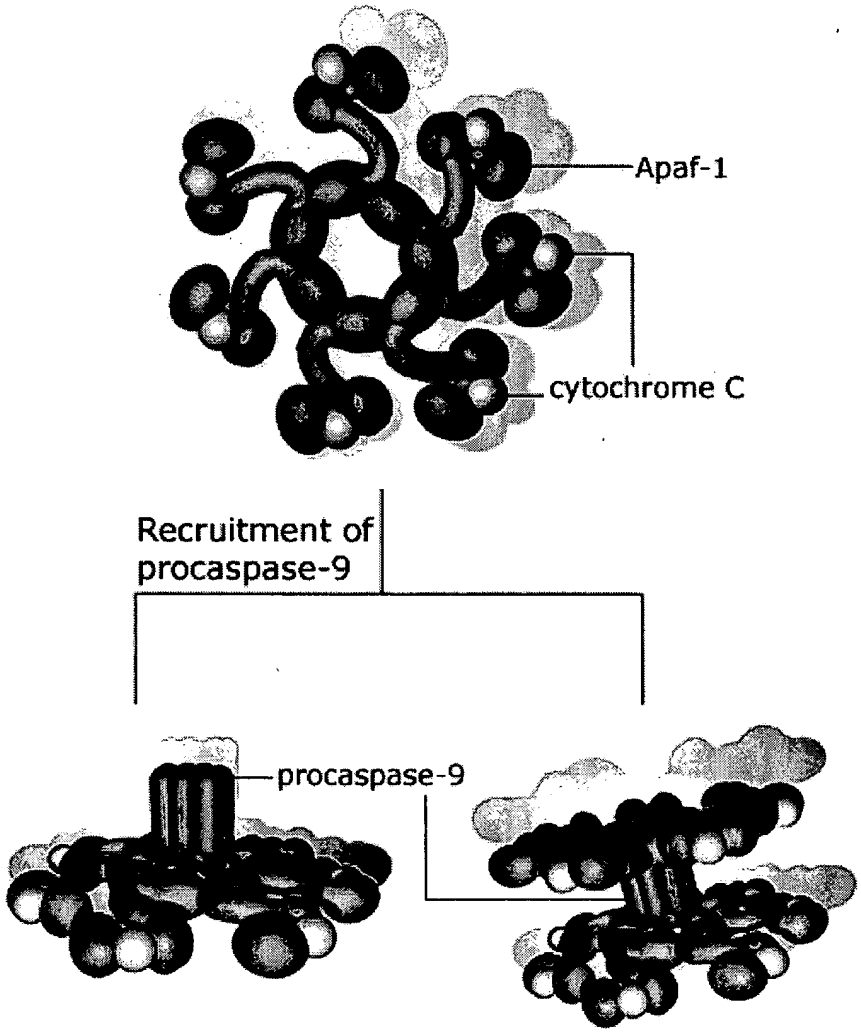
FURTHER INFORMA

Apoptosis
Introduction
Role in disease
Induction
Death Receptors
Role of mitochondr
Bcl-2 proteins
Caspases
Nuclear effects
Role of NO

		HnRNP proteins Topoisomerase I FAK Calpastatin $p21^{Waf1}$ Presenelin2 ICAD	
Caspase-4	Ich-2, $ICE_{rel}II$	Caspase-1	Inflammation/Apoptosis (note: this could be the human form of mouse caspase-11). Related to human caspase-5 and caspase-1
Caspase-5	$ICE_{rel}III$, TY	?	Inflammation/Apoptosis (related to human caspase-4 and caspase-1)
Caspase-6	Mch2	PARP Lamins NuMA FAK Caspase-3 Keratin-18	Apoptosis
Caspase-7	Mch3, ICE-LAP3, CMH-1	PARP Gas2 SREB1 EMAP II FAK Calpastatin $p21^{Waf1}$	Apoptosis (activity blocked by cIAP1 and cIAP2) Similar in structure and substrate specificity to caspase-3
Caspase-8	FLICE, MACH, Mch5	Caspase-3 Caspase-4 Caspase-6 Caspase-7 Caspase-9 Caspase-10 Caspase-13 PARP Bid	Apoptosis (death receptors)
Caspase-9	Apaf-3, ICE-LAP6, Mch6	Caspase-3 pro-Caspase-9 Caspase-7 PARP	Apoptosis
Caspase-10	FLICE-2, Mch4	Caspase-3 Caspase-4 Caspase-6 Caspase-7 Caspase-8 Caspase-9	Apoptosis (death receptors)
Caspase-11	Ich-3, ICE_B	?	Murine caspase similar to human caspase-4. Belongs to the same family as caspase-3 of enzymes. May be involved in inflammation and apoptosis
Caspase-12	ICE_C	?	Involved in mediating apoptosis following ER stress. Related to mouse caspase-1 and caspase-11 and human caspase-4 and caspase-5
Caspase-13	ERICE	?	Member of the ICE family of caspases that include caspase-1 and caspases-4, -5 and -11. Involved in inflammation.

Aside from the ligation of death receptors there are a number of other mechanisms through which the caspase cascade can be activated. Granzyme B can be delivered into cells by cytotoxic T lymphocytes and is able to directly activate caspases 3, 7, 8 and 10. The mitochondria are also key regulators of the caspase cascade and apoptosis. Release of cytochrome C from mitochondria can lead to the activation of caspase 9, and then of caspase 3. This effect is mediated through the formation of an apoptosome, a multi-protein complex consisting of cytochrome C, Apaf-1, pro-caspase 9 and ATP. The formation of the apoptosome is illustrated below.

First stage of apoptosome formation



Caspase Activation

Cytochrome C released from the mitochondria binds to the cytosolic protein Apaf-1. This interaction results in a conformational change in Apaf-1 which, when stabilised by the binding of ATP, allows molecules of Apaf-1 to associate with each other. This results in the formation of a wheel-like

structure that contains 7 molecules each of Apaf-1, cytochrome C and ATP. This wheel-like structure, known as the apoptosome, permits the recruitment of 7 molecules of procaspase-9 to the complex. The exact mechanism of caspase activation is still uncertain although two possibilities have been proposed. In one case the Apaf-1, cytochrome C and procaspase-9 complex can act as a stage to activate cytosolic procaspase-9 as it is recruited to the apoptosome. In the other scenario two apoptosome have been proposed to interact with each other and to activate the caspase-9 located on the other apoptosome.